REMARKS

Applicants request reconsideration of the above-identified application in view of the foregoing amendments and following remarks.

The Claim Amendments

Applicants have amended claims 1, 5-7, 24 and 27-28. Support for the amendments to claim 1 can be found in claims 4, 5 and 26 as originally filed, on specification page 10, line 24 to page 11, line 2, and in Example 1. Support for the amendments to claim 5 can be found in Table 1 on page 33 of the specification.

Applicants have amended claims 6 and 7 to conform their subject matter with that of claim 1 and to correct claim dependencies.

Applicants have amended claim 24 to address the Examiner's rejection. Support for the amendment to claim 24 can be found on page 10, line 24 to page 11, line 2, and in Example 1.

Support for the amendments to claims 27 and 28 can be found in previously filed claims 4 and 26, respectively.

Applicants have added claims 38 and 39. Support for new claims 38 and 39 can be found on page 10, line 24 to page 11, line 2, and in Example 1 of the specification.

Applicants have cancelled claims 4, 26, 36 and 37 and withdrawn claims 8-23 and 29-35. Therefore, claims 1, 3, 5-7, 24, 27-28, 38 and 39 are now pending in this application.

The above amendments are made specifically without waiver of applicants' rights to continue to prosecute and to obtain claims directed to the deleted subject matter either in this application or in other applications.

The Rejections

35 U.S.C. § 101

The Examiner has rejected claims 1, 3-7, 24, 26-28, 36 and 37 as allegedly not supported by a credible, specific and substantial utility or a well established utility. The Examiner states that instant claims are drawn to a transgenic mouse comprising in its genome, a transgene construct comprising a nucleotide sequence operably linked to a promoter which encodes a heterologous amyloid precursor protein 695 (APP695) polypeptide wherein the lysine residue at position 670 is substituted by asparagine, the methionine residue at position 671 is substituted by leucine, and the valine residue at position 717 is substituted by phenylalanine, and wherein said promoter directs central nervous system or neuronal expression of said transgene. The Examiner contends that the specification identifies the following two uses for the claimed mice: 1) the characterization of the pathogenic mechanisms of Alzheimer's disease and 2) the development of diagnostics, therapies, and therapeutic compounds.

The Examiner also states that "[r]egarding the nucleic acid sequence and vector (e.g. claims 27, 28), the specification only provides a single use for these products, which is their use to produce the claimed mouse" and concludes

that the utility of the nucleic acid sequence and vector depends on the utility of the claimed mouse.

The Examiner also contends that with regards to the asserted utility: "the specification fails to demonstrate that the claimed mouse is a model of Alzheimer's disease." The Examiner asserts that while the specification teaches neuropathological and behavioral changes in the claimed mice, nothing in the art or specification teaches that there are any Alzheimer's patients who express APP with both Swedish and Indiana mutations. The Examiner additionally contends that because there are no patients with this etiology, it is not apparent how the claimed mouse is a model for a human disease.

Finally, the Examiner contends that because the specification does not assert a utility which meets the requirements of 35 U.S.C. § 101 for the claimed mice, the nucleic acid sequences and vector used to make the mice, and the method of making the claimed mouse, also lack a utility.

Applicants traverse. As disclosed in the instant specification, studies of the complex etiology of Alzheimer's disease (AD) have shown that the disease is characterized by toxic cerebral amyloid deposits formed from the proteolysis of amyloid beta-peptide (Aß). Such deposits have been attributed to mutations in the amyloid precursor protein (APP) at codon

717 (the "Indiana mutation" wherein a valine is replaced by an isoleucine (V717I)) and mutations at codons 670 and 671 (the "Swedish mutations" wherein a double base pair substitution results in lysine and methionine replaced by aspartic acid and leucine (K670D/M671L)). In order to better understand the role that such plaques may have in the onset and development of AD, applicants have developed an animal model which demonstrate neurological and physical aspects of the disease. For example, this animal model has been used in animal behavioral studies, used to identify disease modifiers, to reproduce specific aspects of the human disease and screen drug candidates for efficacy (see, e.g., Gervais et al., *Neurobiology of Aging*, 28:537-547 (2007) submitted as Appendix A). Those skilled in the art recognize that insight gained from studies involving animal models, such as the transgenic mice of the present invention, can assist in the development of the treatments and therapies for Alzheimer's Disease.

The Examiner states that because there is nothing in the art or specification which teaches that any Alzheimer's patients have both the Swedish and Indiana mutations, that it is not readily apparent how the claimed mouse is a model for a human disease. Applicants submit, however, that a skilled artisan would recognize that the important feature of a

relevant animal model is whether the amyloid pathology of the model resembles that of human Alzheimer's disease and not whether the combination of mutations in the animal is identical to any particular human case of Alzheimer's disease. As the specification discloses on page 10, lines 4-14, the claimed mouse displays abnormal Aß deposition similar to that seen in human patients with Alzheimer's Disease. As a result of these Aß plaques, the claimed mice exhibit both histological and behavioral deficits and display an accelerated appearance of several facets of human AD-related pathology. Thus, as the mice display human AD-related traits, a skilled artisan would be able to use the claimed mouse model to, e.g., characterize the pathogenic mechanisms of Alzheimer's disease or develop diagnostics, therapies, and therapeutic compounds, regardless of whether or not an Alzheimer patient expresses APP with both the Swedish and Indiana mutations.

In addition, the Examiner has asserted that the utility of the claimed nucleic acid sequence and vector depends on the utility of the claimed mouse. Thus, in light of the arguments made above, it is clear that a skilled artisan would find utility for both the claimed nucleic acid

sequence and vector. Therefore, applicants respectfully request that the Examiner withdraw the rejection.

35 U.S.C. § 112, First Paragraph: Enablement

Claims 1, 3-7, 24, 26-28, 36, 37 remain rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the enablement requirement. The Examiner alleges that "nothing in the art or specification provides guidance that any there is any human disease associated with human APP695 comprising both the Swedish and Indiana mutations" and that the claimed mouse is not a model of any human disease and has no readily apparent use.

The Examiner states the claims are broadly drawn to the use of heterologous APP695 comprising the Swedish and Indiana mutations ($APP_{Sw,Ind}$) thus bringing up two issues. The Examiner first states that "an artisan cannot rely on the amino acid residue number as being the amino acid to mutate, as not all APP amino acid sequences from other species of animals have the same residue numbers" and that the specification does not provide guidance as to how to identify corresponding residues in proteins from heterologous animals. The Examiner also states, pointing to Hammer et al. 1986, J. of Anim. Sci., 63: 269-278 ("Hammer"), that at the time of

filing, the art taught that "not all heterologous proteins expressed in transgenic animals predictably have activity." Thus, the Examiner contends that the specification does not provide guidance for use $APP_{Sw,Ind}$ from other species and that an artisan cannot reasonably predict that heterologous proteins will demonstrate predicted activity in transgenic mice.

The Examiner additionally states that rejected claims are broadly drawn to a central nervous system (CNS) or neuronal promoter and that at the time of filing, "the art teaches that not all neural promoters in transgenic mice behave the same." The Examiner points to Andra et al., 1996, Neurobiology of Aging, 17: 183-190 ("Andra") and states that Andra teaches that several neuron-specific promoters can be used to drive expression of human APP in transgenic mice. The Examiner contends that "[w]hile the specification teaches the use of a Syrian hamster prion protein gene promoter (specification, page 4, 4th parag.), the specification does not provide guidance for an artisan to use other neural-specific promoter[s]..."

In addition, the Examiner states that the claims broadly encompass the use of any strain of mouse and that, at the time of filing, "the art teaches that an artisan cannot

predictably arrive at the claimed invention using any strain of mouse." The Examiner points to Carlson et al., 1997, Human Molecular Genetics, 6: 1951-1959 ("Carlson") and contends that Carlson suggests "that the genetic background in mice can result in widely different phenotypes." The Examiner goes on to say that "[w]hile the specification teaches the use of C3HxC57BL6 mice (specification, page 20), the specification does not teach the use of other strains of mice such that an artisan could arrive at the mice exhibiting the phenotypes described in the specification..." and that an artisan is not enabled for the full breadth of any strain of mouse.

The Examiner further points to Hsiao et al., 1995, Neuron, 15: 1203-1218 ("Hsiao") and states that Hsiao teaches that transgenic mice which express human APP_{Ind} can have widely differing phenotypes and that the "phenotypic differences appear to stem from differences in make strain and differences in transgene construct." The Examiner, further states that Chishti, et al., 2001, Journal of Biological Chemistry, 276: 21 562-21 570 ("Chishti") teaches that overexpression of APP above a threshold of about 4x endogenous is necessary for the deposition of amyloid plaques in the CNS and that permissive strain backgrounds and particular APP cassettes were used to avoid the toxic effects associated with these levels of APP

overexpression. Thus, the Examiner contends that the use of any promoter will not allow an artisan to readily arrive at the claimed mouse and that the specification, in turn, does not provide guidance for the artisan to practice the claimed invention for its full breadth.

Finally, the Examiner states that the mice of claim 1 exhibit no phenotype, but that there is nothing in the art or specification which provides guidance on how to use such mice.

Applicants traverse. However, solely to expedite prosecution, applicants have amended claims 1, 5-7, 24, 27 and 28, cancelled claims 4, 26, 36 and 37 and added claims 38 and 39. Amended claim 1 recites a C3H x C57 mouse whose genome comprises a human $APP695_{Sw,Ind}$ transgene operably linked to a cos.Tet promoter wherein said transgenic mouse displays abnormal Aß deposition in its central nervous system. Claim 24, as amended, recites a method for producing such a mouse. Thus, the claims, as amended, overcome the Examiner's rejections.

With regards to the Examiner's assertion that claimed mouse is not a model of any human disease and has no readily apparent use, applicants refer to the arguments made in addressing the 35 U.S.C. § 101 rejection above.

In light of foregoing amendments and arguments, applicants respectfully request that the Examiner withdraw the rejections.

35 U.S.C. § 112, Second Paragraph: Indefiniteness

The Examiner has rejected Claims 6, 24, 26 and 37 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner argues that there is no antecedent basis for the limitation "the animal" in claim 6, that the scope of "animal" is larger than that of "mouse," and that it is unclear as to whether "animal" refers back to the mouse or to a different animal.

Applicants have amended claim 6 to recite "The C3H x C57 mouse of claim 1 wherein the mouse displays..." thus obviating the Examiner's rejection.

The Examiner also argues that claim 24, step d, appears to be missing the word "its" in the phrase "selecting an offspring where genome comprises..." Claims 26 and 37, which depend on claim 24, are also included in the rejection.

Applicants have amended claim 24, step d, to recite "selecting an offspring where its genome comprises..." thus obviating the Examiner's rejection.

Applicants respectfully request that the Examiner withdraw these rejections in view of the amended claims.

35 U.S.C. § 102(b)

Claims 1, 4-7, 24, 27, 28, 36, 37 are newly rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Hsia et al., 1999, PNAS, USA, 96: 3228-3233 ("Hsia") as evidenced by Jin et al., 2004, PNAS, USA, 101, 13363-13367 ("Jin") and Selkoe, 2002, Science, 298: 789-791 ("Selkoe"). The Examiner states that Hsia teaches a transgenic mouse line comprising a transgene construct comprising a nucleic acid sequence encoding human amyloid protein precursor (APP) comprising the Swedish (Sw) and Indiana (Ind) mutations operably linked to a PDGF B chain promoter (which directs expression in the brains of mice). The Examiner further states that Jin teaches that mice made by Hsia expressed the three human APP isoforms, APP695, APP751, and APP 770 and that the Swedish mutation is K670N/M671L and that the Indiana mutation is V717F. The Examiner goes on to state that the $APP_{Sw,Ind}$ mice of Hsia exhibited an Alzheimer's Disease-related pathology by 3 months

of age and that 2-4 month mice exhibited a deficit in synaptic transmission that was twice as large as that in line H6 (APP_{Ind} mice) The Examiner notes that the art teaches that loss of synaptic transmission is one characteristic of Alzheimer's disease. Finally, the Examiner asserts that the instant claims drawn to methods of making the $APP_{Sw,Ind}$ mice are anticipated by Hsia as the reference teaches that the transgene (PDGF-$APP_{Sw,Ind}$) was injected into one-cell embryos of mice.

Applicants traverse. Applicants have amended claims 1, 5-7, 24, 27 and 28, cancelled claims 4, 36 and 37 and added claims 38 and 39. As explained above, amended claim 1 recites a C3H x C57 mouse whose genome comprises a human $APP695_{Sw,Ind}$ transgene operably linked to a cos.Tet promoter wherein said transgenic mouse displays abnormal Aß deposition in its central nervous system. Claim 24, as amended, recites a method for producing such a mouse. The amended claims overcome the Examiner's rejection for the following reasons.

According to the Examiner, Hsia recites transgenic mice (J9) comprising an $APP_{Sw,Ind}$ transgene operably linked to a PDGF promoter. In addition, the mice recited in Hsia were generated from (C57BL/6 x DBA/2) embryos (see page 1, col. 2 under "Transgenic Mouse Lines"). Hsia does not teach C3H x

C57 mice comprising a human $APP695_{Sw,Ind}$ transgene operably linked to a cos.Tet promoter as required by the instant claims. Thus as Hsia does not teach each and every element of the claimed invention, it does not anticipate the instant claims.

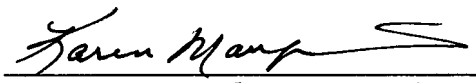
In addition, the claimed transgenic mice display an unexpected improvement over those recited in Hsia. Specifically, page 22, lines 18-20 of the specification and Example 1 teach that the claimed transgenic animals display visible plaque deposits as early as 60 days after birth with robust plaques being visible at 90 days. Such a timeframe for plaque development is a marked improvement over those recited in Hsia. In fact, Hsia specifically recites that "[a]lthough amyloid plaques were found in $APP_{Sw,Ind}$ mice from line J9 at 8-10 months of age, no amyloid plaques were detected in these mice at ages analyzed electrophysiologically (0 of 19 mice at 2-4 months of age) (see page 3232, column 2, first full paragraph; emphasis added). Thus, the claimed transgenic mice displays a desirable phenotype in a much shorter timeframe than the J9 mice of Hsia.

Applicants respectfully request that the Examiner withdraw the rejection in view of the amended claims and arguments above.

CONCLUSION

For all of the above reasons, applicants request that the Examiner reconsider and withdraw the outstanding objections and rejections, enter the amendments, and pass the resulting claims to allowance.

Respectfully submitted,



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